

### **REMARKS/ARGUMENTS**

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance. Examiner Woolwine is thanked for considering Claims 1-9 and 73-75 to be allowable.

#### **Status of the Claims and Formal Matters**

Claims 1-84 are currently pending in this application. Of these, Claims 10-39, 41-46, and 65-71 were deemed withdrawn as allegedly being drawn to a non-elected invention. By this paper, Claims 8, 10-72, and 76 to 84 have been cancelled and Claims 1 and 73-75 has been amended, without prejudice and solely in an effort to expedite prosecution pursuant to the U.S. Patent and Trademark Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)). Applicants assert the right to reclaim withdrawn or cancelled subject matter in co-pending applications. No new matter has been introduced by these amendments. Support for the amendments to Claims 1 and 73-75 can be found throughout the instant specification as originally filed.

The amendments as presented herein are not made for purposes of patentability within the meaning of §§101, 102, 103, or 112. Rather, these amendments are made for clarity and to round out the scope of protection to which Applicants are entitled.

#### **Rejections under 35 U.S.C. §112, 2<sup>nd</sup> Paragraph**

Claims 47-51 and 76-84 were rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regard as the invention.

In particular, Claims 47 and 76 allegedly recite the limitation “the well.” The Office Action contends there is insufficient antecedent basis for this term in the claims.

Claim 80 was rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 80 allegedly recites the limitation “the amplifying step.” The Office Action contends there is insufficient antecedent basis for this recitation in the claims.

Claim 64 was rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 64 allegedly recites the limitation “said PPI—detection enzyme.” The Office Action contends there is insufficient basis for this limitation in the claims.

By this paper, Claims 47-51, 64, and 76-84 have been cancelled, without prejudice, thereby obviating this rejection. Consequently, Applicants respectfully request reconsideration and withdrawal of the §112, 2<sup>nd</sup> paragraph rejection.

**Rejections under 35 U.S.C. §102(e)**

Claims 40, 52, 53, 59-61, and 72 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Weiner et al (U.S. Patent Application Publication No. 2005/0009022; “Weiner”). The Office Action contends that Weiner teaches a method for delivering a bioactive agent to an array, comprising dispersing over the array a plurality of mobile solid supports each having at least one reagent immobilized thereon, wherein the reagent is suitable for use in a nucleic acid sequencing reaction. In view of the amendments cancelling Claims 40, 52, 53, 59-61 and 72, Applicants respectfully submit that the instant rejection is now rendered moot. Reconsideration and withdrawal of the §102(e) rejection over Weiner are respectfully requested.

Claims 47-51 and 62-64 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Rothberg et al (U.S. Patent Application Publication No. 2003/0068629; “Rothberg”). Rothberg allegedly teaches a method for carrying out separate parallel common reactions in an aqueous environment comprising delivering a fluid containing at least one reagent to an array, wherein the array comprises a substrate comprising at least 10,000 discrete reaction chambers, each reaction chamber adapted to contain analytes and wherein the reaction chambers have a volume of between 10 to 150 pL. Claims 47-51 and 62-64 have been cancelled, thereby obviating the rejection. Consequently, Applicants respectfully request reconsideration and withdrawal of the §102(e) rejection over Rothberg.

Claims 76, 80-82, and 84 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Chee et al (U.S. Patent Application Publication No. 2003/0108867; “Chee”). According to the Office Action, Chee allegedly teaches a method for sequencing nucleic acids comprising fragmenting large template nucleic acid molecules to generate a plurality of fragmented nucleic acids, attaching one strand of a plurality of the fragmented nucleic acids

individually to beads to generate single stranded nucleic acid attached individually to beads, delivering a population of the single stranded fragmented nucleic acids attached individually to beads to an array of at least 10,000 reaction chamber on a planar surface, wherein a plurality of the wells comprise no more than one bead with one single stranded fragmented nucleic acid, and performing a sequencing reaction simultaneously on a plurality of the reaction chambers. In view of the cancellation of Claims 76-84, Applicants respectfully request reconsideration and withdrawal of the §102(e) rejection over Chee.

**Rejections under 35 U.S.C. §103(a)**

Claims 40, 52-55, 59-63, and 77 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Wolber (U.S. Patent No. 6,284,465; “Wolber”). The Office Action contends that it allegedly would have been *prima facie* obvious to one of ordinary skill in the art to fabricate the wells in the planar substrate of Chee to achieve a center-to-center spacing of 20 to 100 microns. One allegedly would have been motivated to do so in view of Wolber, who teaches spacing the features on a microarray at “less than or equal to two feature diameters, and preferably 1.5 to 2 feature diameters center-to-center spacing.” The Office Action further alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to fabricate the wells in the planar substrate of Chee to arrive at a width in at least one dimension of between 20 and 70  $\mu\text{m}$ , and it allegedly would also have been obvious to make the wells to correspond to the size of the beads. Applicants respectfully note that the instant rejection is rendered moot in view of the cancellation of Claims 40, 52-55, 59-63, and 77. Reconsideration and withdrawal of the §103(a) rejection over Chee in view of Wolber are respectfully requested.

Claims 47-51 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Kambara et al (U.S. Patent Application Publication No. 2001/0024790; “Kambara”). The Office Action contends that while each of the limitations set forth in the Office Action relating to the dimensions of the reaction chambers and washing the fluid from the array in a specified time period was not expressly taught by Chee, it allegedly would have been obvious to one of ordinary skill in the art at the time the invention was made to design the reaction chambers such that the time required for the reagent to diffuse out of the reaction chamber exceeded the time required for the reagent to react with the starting material, because

otherwise the reagent would diffuse out of the well before completion of the reaction. According to the Office Action, a complete reaction in pyrosequencing was known to be important to one of ordinary skill in the art as evidenced by Kambara, who allegedly teaches that if the reactions are not thoroughly carried out, reactions for each DNA chain proceed unevenly, which interferes with base sequencing. In view of the cancellation of Claims 47-51, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection over Chee in view of Kambara.

Claims 56-58 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Wolber and further in view of Kamb et al (U.S. Patent Application Publication No. 2002/0172965; "Kamb"). The Office Action contends that it would have been *prima facie* obvious to one of ordinary skill in the art to produce the beads with a single species of oligonucleotide to use in the method of Chee by following the method for synthesizing such beads as disclosed by Kamb, since Chee allegedly teaches that target sequences may be prepared using "known techniques", and since Kamb allegedly demonstrates his method was a known, effective, and efficient way for producing such beads. The Office Action further alleges that it would have been equally obvious to perform the bead-based PCR before or after the beads were dispersed on the array. One of ordinary skill in the art allegedly would have easily appreciated that the beads produced by Kamb were structurally identical to the beads used in the method of Chee, even though Kamb uses his beads in a different method. By this paper, Claims 56-58 have been cancelled, thereby obviating this rejection. Reconsideration and withdrawal of the §103(a) rejection over Chee in view of Wolber and Kamb are respectfully requested.

Claim 64 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Wolber and further in view of Nyren et al. The Office Action alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to practice the method suggested by the combined teachings of Chee and Wolber and substitute a dATP or ddATP analogue. The Office Action further contends that the motivation to do so is clearly provided by the disclosure of Nyren to overcome the problem of interference in the luciferase reaction. In view of the cancellation of Claim 64, Applicants respectfully submit that the instant rejection is now moot. Reconsideration and withdrawal of the §103(a) rejection over Chee in view of Wolber and Nyren are respectfully requested.

Claim 72 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Walt et al (U.S. Patent No. 6,023,540; "Walt"). According to the Office Action,

it allegedly would have been *prima facie* obvious to one of ordinary skill in the art to use a CCD camera as taught by Walt to detect the signals from the fiber optic array in the method of Chee, since Chee allegedly desires parallel detection of reactions at individual sites on his fiber optic bundle array and Walt allegedly demonstrates that a fiber optic bundle array connected to a CCD camera achieves this result. The Office Action further contends that Walt allegedly teaches the same basic fiber optic bundle array as Chee, complete with microspheres residing in wells etched in the ends of the fibers, and by using a CCD camera connected to the fiber optic bundle array of Chee, one of skill in the art would allegedly have arrived at the claimed invention. By this paper, Claim 72 has been cancelled, thereby obviating the rejection. Reconsideration and withdrawal of the §103(a) rejection over Chee in view of Walt are respectfully requested.

Claim 78 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Nyren. The Office Action contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use fragments within the range of 30 to 500 bases in the method of Chee, because Nyren allegedly demonstrates that this was a suitable size for pyrophosphate sequencing of bead-immobilized fragments of nucleic acids. In view of the cancellation of Claim 78, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection over Chee in view of Nyren.

Claim 79 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee in view of Nyren and further in view of Kamb. According to the Office Action, it would have been *prima facie* obvious to one of ordinary skill in the art to produce the beads with a single species of oligonucleotide to use in the method of Chee by following the method for synthesizing such beads as allegedly disclosed by Kamb, since Chee allegedly teaches that the target sequences may be prepared using "known techniques" and since Kamb allegedly demonstrates that his method was a known, effective, and efficient way for producing such beads. The Office Action further contends that it would have been equally obvious to perform the bead-based PCR before or after the beads were dispersed on the array. Further, the Office Action states that one of ordinary skill in the art allegedly would have easily appreciated that the beads produced by Kamb were structurally identical to the beads used in the method of Chee, even though Kamb uses his beads in a different method. Applicants respectfully contend that, in view of the cancellation of Claim 79, the instant rejection is now moot. Reconsideration and

withdrawal of the §103(a) rejection over Chee in view of Nyren and Kamb are respectfully requested.

**CONCLUSION**

Favorable action on the merits is respectfully requested. If any discussion regarding this Response is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Respectfully submitted,

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